

Short-term antihypertensive efficacy of perindopril according to clinical profile of 3,188 patients: A meta-analysis

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Abstract

Background: *Perindopril, a long-acting angiotensin converting enzyme-inhibitor, reduces incidence of cardiovascular end points in a wide range of patients. This effect depends on both the antihypertensive and blood pressure lowering unrelated effects. The aim of the study was to check the possible influence of patients' clinical profile on the antihypertensive efficacy of perindopril.*

Methods: *A meta-analysis of individual data of hypertensive patients enrolled in five open studies tested the efficacy and safety of perindopril over a 12-week treatment period.*

Results: *We included data of 3,188 men (39%) and women, aged on average 53 years, whose baseline systolic/diastolic blood pressure averaged 163/99 mm Hg and on average declined by 27/17 mm Hg. Mean duration of hypertension was five years, and 34% of patients had prior cardiovascular complications. We found no difference in the antihypertensive effect of perindopril in patients with complicated vs non-complicated hypertension (Δ SBP 0.05, 95%CI: -1.5 to 1.6 mm Hg, $p = 0.95$), in older vs younger patients (Δ SBP 2.4, 95%CI: -3.2 to 7.9 mm Hg, $p = 0.41$), in men vs women (Δ SBP -1.43, 95%CI: -3.4 to 0.5, $p = 0.15$), and in patients with long-lasting vs shorter duration of hypertension (Δ SBP 0.0, 95%CI: -1.0 to 1.0 mm Hg, $p = 1.0$). The antihypertensive effect of perindopril was stronger in patients with greater (≥ 160 mm Hg) systolic blood pressure (Δ SBP 12.3, 95%CI: 5.5 to 19.0, $p = 0.0004$). The effect on diastolic blood pressure tended to be greater in younger patients (Δ DBP -0.63, 95%CI: -1.2 to -0.02 mm Hg, $p = 0.04$).*

Conclusions: *Perindopril is an effective antihypertensive medication. Its efficacy seems not to be adversely affected by the clinical profile of the patient. (Cardiol J 2010; 17, 3: 259–266)*

Key words: perindopril, hypertension, meta-analysis, efficacy

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Received: 12.07.2009

Accepted: 30.10.2009

Introduction

What is known on the topic? Blood pressure reduction translates into improvement of cardiovascular prognosis in hypertensive patients. The angiotensin converting-enzyme inhibitor perindopril is a potent antihypertensive drug. Accordingly, it reduces the cardiovascular risk both in primary and secondary prevention setting. However, due to the prerequisites of the way clinical trials are conducted, most of the studies that prove this have been performed in highly selected groups of patients, whose clinical characteristics usually differ from those encountered in regular practice.

What this article adds? Building on a large pool of individual patient data from studies performed in a regular outpatient setting, this paper attempts to check whether the antihypertensive effect of perindopril could be influenced by such characteristics as gender, age, baseline systolic blood pressure (SBP), duration of hypertension and history of cardiovascular disease. We found the short-term antihypertensive effect of perindopril to be universal, largely independent of the studied characteristics.

Hypertension is the predominant risk factor for developing cardiovascular complications worldwide [1, 2], both in primary prevention setting and in patients with coronary artery disease and cerebrovascular disease [3]. Cardiovascular risk associated with hypertension can be minimised by adequate antihypertensive treatment [4, 5]. Although some drug classes, angiotensin-converting enzyme inhibitors (ACE-I) in particular, express their beneficial effect through properties extending beyond their effect on blood pressure, in hypertensive subjects it is the reduction of blood pressure which is responsible for most of the protective effect [6]. However, the extent to which the antihypertensive effect depends on patients' characteristics such as baseline blood pressure level, sex, age, and history of cardiovascular complications, has not been sufficiently studied.

In recent years, the results of large-scale trials have been published, showing that perindopril, a long-acting ACE-I, is very potent in reducing the risk of recurrent stroke [7] or new cardiovascular complications in high risk patients [8]. However, patients recruited in the framework of clinical trials usually form a highly selected population.

Based on individual patient data obtained from unselected groups of hypertensive patients, we aimed to check to what extent blood pressure can be lowered during short-term treatment with es-

calated doses of perindopril, and whether this blood pressure reduction would be influenced by clinically relevant characteristics of the patient.

Methods

Data acquisition

We included individual patient data accumulated in the framework of five open-label, multicenter studies performed in Poland between 1994 and 2003. The protocols of the studies were in accordance with the regulations of clinical study conduct in operation at the time the respective studies began. All patients gave informed consent and were subsequently treated with an open label active antihypertensive drug in accordance with its registration characteristics. All trials were supported by unrestricted research grants from Servier Poland, and were carried out by independent clinicians under the supervision of experts in the field of hypertension with high academic and clinical profiles. After the respective databases had been closed, the data were analyzed and published in a range of Polish medical journals. Subsequently, the data were stored by Servier Poland in the MS Excel format. In order to perform the current analysis, the data were converted into SAS format. The subsequent cleaning, merger, management, and analyses of data, were performed by one of the authors (J.G.) using SAS 9.1 software, independently of Servier Poland.

Subgroup definition and selection of outcome measures

We defined the subgroups in which we tested the short-term antihypertensive efficacy of perindopril as 'progressors' and 'non-progressors' (patients who at the end of respective studies were receiving 8 and 4 mg of perindopril per day, respectively), non-complicated and complicated hypertension (history of one or more of the following: coronary artery disease, myocardial infarction, stroke, and heart failure), older or younger than median age in the total population, sex, SBP of less than or of 160 mm Hg and more, shorter or longer (than population median) duration of hypertension. As a primary outcome measure, we chose the treatment-induced change in SBP. As a secondary outcome measure, we used the treatment-induced change in diastolic blood pressure (DBP).

Statistical analysis

We used the SAS software package (SAS Institute, Cary, NC), version 9.1, and Review Manager 4.2 (Cochrane Collaboration, Copenhagen,

Table 1. Characteristics of patients.

Characteristic	PAS12 (n = 1806)	PAS3 (n = 378)	PAS4 (n = 622)	PADS (n = 379)	All (n = 3188)
Sex — male (%)	49.3	47.6	0	45.8	39.0
Age (years)	51.6 ± 10.6	50.0 ± 9.2	54.8 ± 5.4	55.9 ± 8.2	52.5 ± 9.5
HT duration (years)	5.8 ± 5.3	4.1 ± 4.9	3.6 ± 4.7	5.3 ± 5.2	5.1 ± 5.3
BP [mm Hg]:					
Baseline SBP	168.0 ± 17.7	161.6 ± 10.0	161.9 ± 9.3	148.5 ± 6.1	163.7 ± 15.8
Follow-up SBP	140.3 ± 13.9	136.5 ± 10.1	136.3 ± 9.9	124.5 ± 8.4	137.2 ± 13.2
ΔSBP	27.7 ± 18.4	25.1 ± 12.2	25.6 ± 11.0	24.0 ± 10.0	26.5 ± 15.7
Baseline DBP	101.7 ± 8.5	99.3 ± 5.2	98.3 ± 5.3	90.2 ± 4.7	99.4 ± 8.1
Follow-up DBP	85.6 ± 8.4	83.6 ± 6.3	82.2 ± 5.8	77.9 ± 5.7	83.8 ± 7.8
ΔDBP	16.1 ± 10.6	15.6 ± 7.6	16.6 ± 6.9	12.3 ± 6.6	15.6 ± 9.3
Complications (%):	41.5	30.7	28.0	15.0	34.4
CAD	9.5	8.7	9.6	9.2	9.4
MI	1.8	0	0.5	1.3	1.3
HF	1.1	0	0	0.3	0.6
ST	0.6	0	0.3	0.8	0.5
Dose of perindopril at follow-up	5.0 ± 1.8	4.8 ± 2.1	5.4 ± 2.2	5.4 ± 2.1	5.1 ± 2.0
Indapamide (%)	13.7	7.9	13.4	10.3	12.5

Plus-minus values are non-weighted mean ± standard deviation; HT — hypertension; BP — blood pressure; SBP — systolic blood pressure, DBP — diastolic blood pressure; Δ — difference between baseline and follow-up; CAD — coronary artery disease; MI — myocardial infarction; HF — heart failure; ST — stroke

Denmark), for database management and statistical analysis. We compared means and proportions by the standard normal z-test and the χ^2 -statistic, respectively. Using random effects modeling, we calculated the net difference in blood pressure lowering effect according to defined subgroups. The heterogeneity was checked using Zelen's test (based on χ^2 distribution) and I^2 statistic. I^2 of more than 50% was considered to indicate significant heterogeneity of the effect across studies. The time trends of blood pressure change from baseline and the time subgroup interaction were checked using the ANOVA models, as implemented in the PROC GLM procedure of SAS software. In cases of significant heterogeneity across studies, the influence of a characteristic on studied outcome was checked using ANOVA models with adjustment for respective study.

Results

Characteristics of studies

In the analysis, we included individual data of 3,188 patients enrolled in five open-label studies which assessed the efficacy and tolerability of 2 to 8 mg of perindopril daily. The main characteristics of the studies are presented in Table 1. The two largest studies were the Perindopril Assessment

Study phase 1 and 2 (PAS12), performed between 1994 and 1996 [9]. The studies were performed according to the same protocol and the databases were pooled soon after their completion, and therefore are considered jointly. The inclusion criteria were based on the level of DBP. Included were consecutive outpatients or newly diagnosed untreated hypertensives, whose DBP was in the range between 90 to 110 mm Hg. The treatment period of the study lasted for 15 weeks. The data of 1,806 patients (out of a total 2,038), were available for the present analysis. The Perindopril Assessment Study 3 (PAS3) took place between 1997 and 1998 [10]. The blood pressure inclusion criteria were based on elevation of SBP (140–179 mm Hg) and/or DBP (90–99 mm Hg). To be included, the untreated or uncontrolled hypertensives had to have body mass index (BMI) of more than 30 kg/m². The treatment period of the study lasted 12 weeks. Of 391 enrolled, the data of 378 patients were available at the end of follow-up and included in the present analysis [10]. The Perindopril Assessment Study 4 (PAS4) was performed between 1998 and 1999 in a group of 667 post-menopausal women [11]. The blood pressure entry criteria were the same as for the PAS3. After the 12 week treatment period, the data of 622 patients were available for analysis. Finally, the Perindopril Assessment in Diabetes Study

(PADS) was performed between 2002 and 2003 in 400 patients in whom diabetes mellitus had been diagnosed at least three months prior to inclusion, and whose SBP values were in the range of 135 to 159 mm Hg, or whose DBP values were in the range of 85 to 99 mm Hg [12]. After the treatment period of 12 weeks, the data of 376 patients were available for analysis.

In all studies, the included subjects were consecutive outpatients who met the entry criteria. In all patients who after the run-in period of two weeks met the criteria, treatment with perindopril 2 to 4 mg once daily was started. During consecutive visits performed at four week intervals, the physicians could raise the dose of perindopril (up to 8 mg once daily) as judged necessary to achieve the pre-defined blood pressure control. Only after the maximum dose of perindopril was reached could the physician in charge introduce the second-line drug, a thiazide-like diuretic indapamide (2.5 mg standard release, or 1.5 mg sustained release preparation, once daily). In patients whose blood pressure was uncontrolled despite receiving the maximal treatment as provided for in the protocol of the study, or in whom there were compelling indications for other treatments or for withdrawal from the study, the protocol-based treatment was stopped and the appropriate action taken (Table 1). In four studies, the target was the DBP of less than 90 mm Hg. In the PADS, the target was blood pressure of less than 135/80 mm Hg.

Characteristics of patients

Except in the one study (PAS4) which included only women, the percentage of men was 45.8 to 49.3, and overall, women predominated in the pooled database (61.0%). Mean age of the analyzed subjects ranged from 50.0 to 55.9 years and averaged (weighted for the size of study) 52.1 years. A total of 1,501 (47.1%) patients were older than the median age of 53.0 years. The average duration of hypertension was 5.1 ± 5.3 years. In 1,503 (47.2%) patients, the duration of hypertension was longer than the overall group median of 3.4 years. At baseline, 1,098 (34.4%) patients had complications of hypertension. In 2,014 (63.2%) patients, the baseline SBP was higher than 160 mm Hg. The average dose of perindopril at the end of the treatment period was 5.1 mg (range 2–8). At that time, 2,092 (65.6%) patients were receiving 4 mg of perindopril once daily (dose non-progressors) and 923 (29.0%) were treated with 8 mg of perindopril once daily (dose progressors). At the end of follow-up, 400 (12.6%) patients were additionally receiving indapamide. The

doses of 2 and 6 mg were received by 61 (1.9%) and 41 (1.3%) patients respectively. In 71 (2.2%) patients the protocol-based treatment was stopped at the last visit. The goal level for systolic, diastolic or both blood pressures was achieved in 53.5%, 68.6%, and 43.9% of patients, respectively (Table 1).

Blood pressure lowering in dose progressors and non-progressors

The baseline SBP and DBP was significantly higher ($p < 0.0001$) in 613 patients who in the course of a study required an increase in the dose of perindopril to 8 mg, and were not concomitantly treated with indapamide (progressors, $165.8 \pm 16.2/100.7 \pm 8.0$ mm Hg) as compared with 2,016 patients who at the end of a study were treated with perindopril 4 mg, without additional indapamide (non-progressors, $162.0 \pm 15.3/98.5 \pm 7.9$ mm Hg). At the end of the 12 week treatment phase, the SBP and DBP in progressors ($138.8 \pm 12.5/84.8 \pm 7.6$ mm Hg) were higher ($p < 0.0001$) than in non-progressors ($135.1 \pm 12.3/82.5 \pm 7.2$ mm Hg). Using the multivariate ANOVA approach, with adjustment for trial allocation, we found that the time-course of blood pressure decrease was faster in progressors and that the progression to 8 mg was associated with a higher degree of net blood pressure change (all $p < 0.0001$). At first, second and last follow-up visits the net blood pressure differences of SBP from baseline, in progressors minus non-progressors (95%CI, p) were: -6.9 (-7.5 to -6.9 , $p < 0.0001$), -1.5 (-2.0 to -0.9 , $p = 0.03$) and 0.2 (-0.3 to 0.8 , $p = 0.68$), respectively. For the rest of the analyses, we considered the patients' data irrespective of the dose progression status.

Blood pressure lowering according to clinical profile

Using the random effects model for continuous outcome measures as implemented in the Review Manager version 4.2 (Cochrane Collaboration), we checked whether the antihypertensive effect of perindopril was influenced by patients' clinical profile. We performed this analysis for five pre-defined clinical characteristics: complicated vs non-complicated hypertension, long vs short duration of hypertension, men vs women, older vs younger, and with or without elevation of SBP above 160 mm Hg. To do that, for each of the subgroups, and in each study separately, we calculated the blood pressure difference (standard deviation) between last and first visit during the treatment phase. We also checked for the possible heterogeneity of the effect across the trials using the Zelen's test and I^2 statistic.

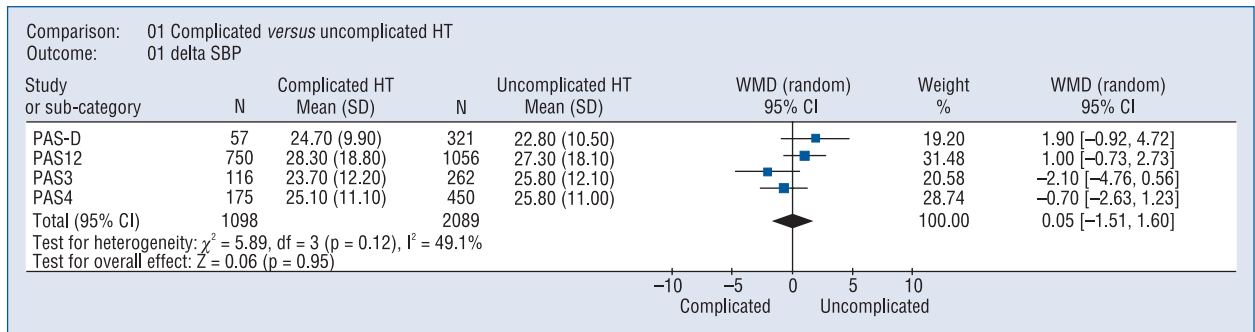


Figure 1. Comparison 1. Complicated *versus* non-complicated hypertension (HT).

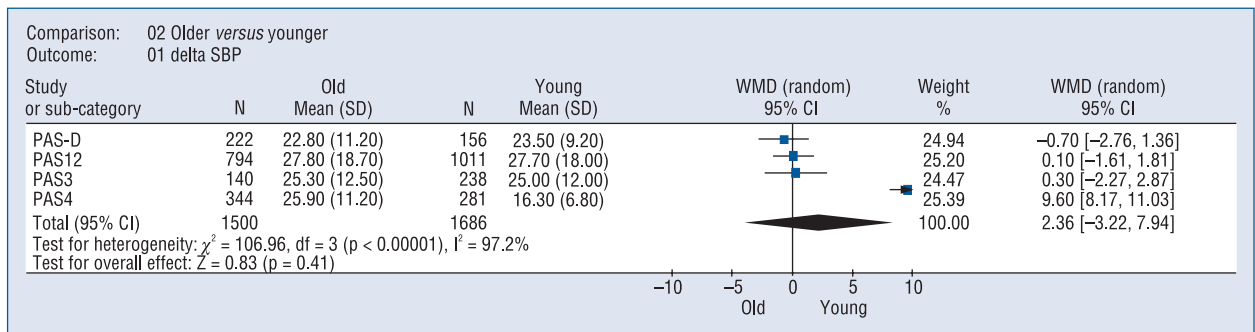


Figure 2. Comparison 2. Older *versus* younger patients.

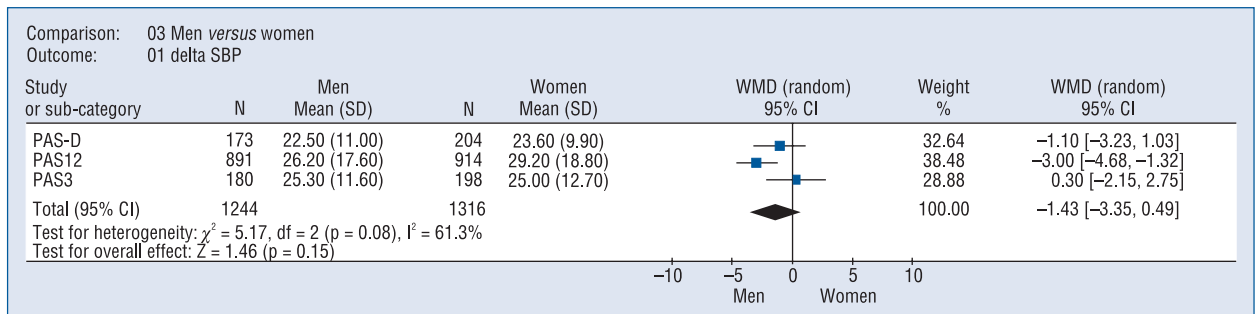


Figure 3. Comparison 3. Women *versus* men.

Overall, there was no difference in the antihypertensive effect of perindopril in patients with complicated hypertension as compared to those without complications (Δ SBP 0.05, 95%CI: -1.5 to 1.6 mm Hg, $p = 0.95$, $I^2 = 49.1\%$, Fig. 1), in older compared to younger patients (Δ SBP 2.4, 95%CI: -3.2 to 7.9 mm Hg, $p = 0.41$, $I^2 = 97.2\%$, Fig. 2), in men compared to women (Δ SBP -1.43, 95%CI: -3.4 to 0.5, $p = 0.15$, $I^2 = 61.3\%$, Fig. 3), and in patients with long-lasting compared to shorter duration of hypertension (Δ SBP 0.0, 95%CI: -1.0 to

1.0 mm Hg, $p = 1.0$, $I^2 = 0\%$, Fig. 4). When the elevation of SBP (≥ 160 mm Hg compared with < 160 mm Hg) was considered, the antihypertensive effect of perindopril was stronger in the group with SBP ≥ 160 mm Hg (Δ SBP 12.3, 95%CI: 5.5 to 19.0, $p = 0.0004$, $I^2 = 97.5\%$, Fig. 5).

For age, sex and SBP elevation classes (I^2 greater than 50%), we repeated the analysis using the multivariate ANOVA with adjustment for trial allocation. For age and SBP groups it yielded confirmatory results (the p values for the class time

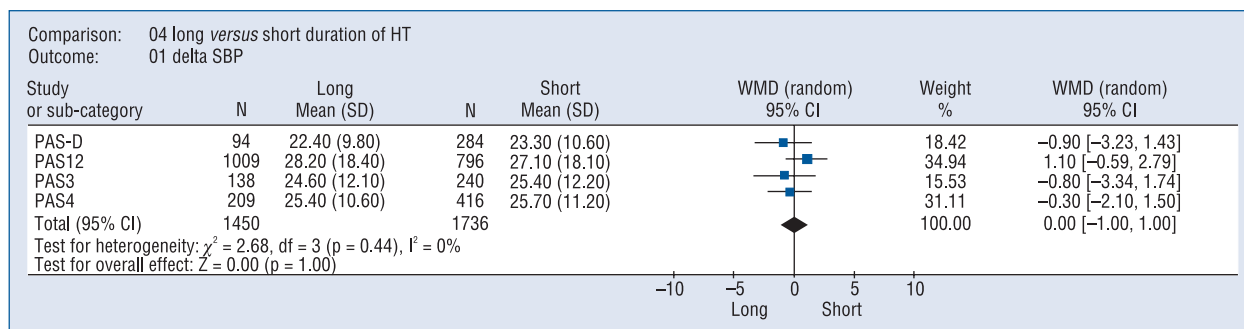


Figure 4. Comparison 4. Long versus short duration of hypertension (HT).

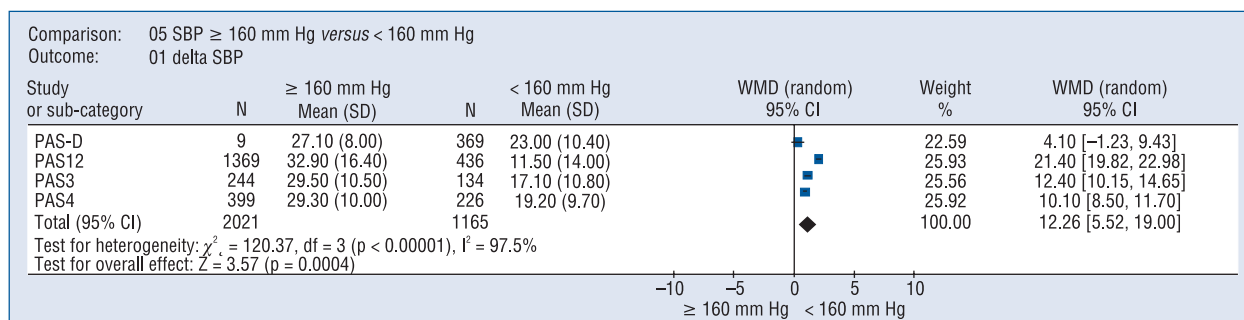


Figure 5. Comparison 5. Higher versus lower systolic blood pressure (HT).

interaction and the between-subject overall trend differences of 0.89 and 0.63, respectively, for age, and 0.0001 and 0.0001 respectively, for SBP). For sex classes, the analysis showed a significant between-subject difference in achieved blood pressure reduction favouring women (adjusted Δ SBP -2.7 , 95%CI: -2.9 to 2.5 , $p = 0.004$); however, there was no influence of sex class on the time-related slope of SBP decrease ($p = 0.30$). The effect of treatment with perindopril on DBP was influenced by age. In younger patients, there was a significant trend for greater effect (Δ DBP -0.63 , 95%CI: -1.2 to -0.02 mm Hg, $p = 0.04$, $I^2 = 0\%$). Likewise, in patients with baseline SBP equal or higher than 160 mm Hg (with mean baseline DBP of 102.2 ± 7.2 mm Hg), compared to patients with SBP lower than 160 mm Hg (baseline DBP 94.5 ± 7.3 mm Hg), the effect of treatment with perindopril on DBP was greater (adjusted Δ DBP -4.5 , 95%CI: -5.2 to -7.6 mm Hg, $p < 0.0001$).

Discussion

Our meta-analysis of individual patient data demonstrates that perindopril, an ACE-I, efficiently reduces blood pressure in patients irrespective of their main clinical characteristics. This blood pressure-lowering effect is not substantially altered by

the presence of complications, age, sex, or duration of hypertension. The effect is more pronounced in patients with higher SBP values. The slope of the decrease of blood pressure is steeper in patients who progress to higher doses of perindopril. However, both progressors and non-progressors achieve substantial blood pressure reductions.

Perindopril was shown to be an effective antihypertensive agent. In essential hypertensive patients, it is capable of reducing blood pressure by 22/11 mm Hg, SBP and DBP, respectively [13]. It was shown to be non-inferior in this capacity to placebo [13], and a range of antihypertensive medications, including beta blockers [14, 15], diuretics [16], and other angiotensin converting enzyme inhibitors [17]. On the other hand, treatment with perindopril was shown to be safe, even in patients with mild or no elevation of blood pressure [18].

The issue of the antihypertensive efficacy of perindopril in a large population of hypertensive patients has been addressed in a large practice-based study carried out in the USA [19]. The study, which included more than 13,000 patients, showed that on average, perindopril reduced blood pressure from 156.9/84.5 mm Hg to 139.2/84.0 mm Hg. In line with this observation, we showed a similar degree of blood pressure lowering effect associated

with up-to 12 week treatment with perindopril. In a series of further sub-studies, the investigators showed that perindopril effectively reduces blood pressure in patients with cardiovascular disease, isolated systolic hypertension and patients with previously refractory hypertension [20]. Contrary to some reports from smaller studies [21], the investigators also showed that it is likewise efficacious in older hypertensive patients [22]. In our meta-analysis, we were able to confirm and extend these findings. We demonstrated that perindopril is equally effective in patients with and without cardiovascular complications. We also showed that it tends to be more effective in patients with higher SBP. However, neither age nor sex nor duration of hypertension influenced its short-term antihypertensive potency.

The present study must be interpreted within the context of its limitations. Although the data we used were collected uniformly, there were differences in protocol regarding the blood pressure criteria for entry. One of the included studies recruited only post-menopausal women ; another was performed in obese hypertensives; and yet another one in diabetic patients with hypertension. This may have influenced the blood pressure, responsiveness to therapy, and prevalence of cardiovascular complications. Secondly, in our post-hoc analysis we categorised patients according to their clinical profile, which was not provided for in the protocols of the respective trials. The effect of the unadjusted analyses of the effect of one characteristic on blood pressure reduction, may contain an effect of another (i.e. the effect of SBP may contain an effect of age). This may (and for some clinical characteristics indeed does) cause heterogeneity of the effect. However, the repeated analyses using ANOVA with adjustment for trial allocation give largely confirmatory results. Lastly, the perindopril formulation used in the included studies (4 mg tablets) differed from the formulations currently available on the market (5 mg and 10 mg tablets).

Conclusions

In conclusion, in a large cohort of mild-to-moderate hypertensive patients, we confirmed that perindopril is an effective blood pressure-lowering medication, and in patients with higher SBP its potency seems to be somewhat higher. The drug is equally efficacious and safe in patients with and without cardiovascular complications, women and men, older and younger and those with either short or longer duration of hypertension.

Acknowledgements

The studies included in the present analyses were sponsored by Servier Poland.

Dr Gąsowski's input was, in part, supported by an unrestricted educational grant of 1,250 EUR from Servier Poland. Dr Wilkins is an employee of Servier Poland, the sponsor of studies included in the analyses.

J.G., T.G. and A.W. had the idea for this analysis. A.W. administered the databases and supervised the quality and acquisition of data in respective studies, and supplied the logistic support. J.G. pooled the databases, designed and performed statistical analyses and drafted the manuscript. J.G. and T.G. prepared the final version of the manuscript. J.D., J.K., Z.G. and M.K. took part in designing, and were principal investigators of the included studies. All authors have seen, critically commented on, and approved the final version of the manuscript and declare that they have no conflict of interest regarding its matter.

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